Amendments to the Specification:

Please amend the paragraph on page 3, line 11, through page 4, line 24, beginning, "Specifically, the present invention relates to primary cultured..." as follows:

--Specifically, the present invention relates to primary cultured adipocytes for gene therapy, which stably hold a foreign gene(s) encoding a protein(s) that is secreted outside of the cell, methods of producing these cells, implant compositions comprising these cells, the use of these cells, and the like, and more specifically to:

[1] a primary cultured adipocyte for gene therapy, wherein the adipocyte stably maintains a foreign gene encoding a protein that is secreted outside of a cell;

[2] the adipocyte of [1], wherein the gene is transferred to the cell by a retroviral vector or adeno-associated viral vector;

[3] the adipocyte of [1], which has the ability to significantly express the protein *in vivo* for at least 20 days;

[4] the adipocyte of [1], which is used to release the protein into the blood flow;

[5] the ~~method~~ adipocyte of [1], wherein the protein is insulin or glucagon-like peptide 1 (GLP-1);

[6] a method of producing an adipocyte for gene therapy, wherein the method comprises the steps of:

(i) primary culturing an adipocyte; and

(ii) transferring, and then stably holding a foreign gene encoding a protein that is secreted outside of the cell;

[7] the method of [6], wherein the foreign gene is transferred by a retroviral vector or adeno-associated viral vector;

[8] an adipocyte for gene therapy, which is produced by the method of [6] or [7];

[9] an implant composition for gene therapy, wherein the composition comprises a primary cultured adipocyte, which stably holds a foreign gene encoding a

protein that is secreted outside of the cell, and a pharmaceutically acceptable carrier;

[10] the implant composition of [9], which further comprises an extracellular matrix component;

[11] the implant composition of [9], which further comprises an angiogenesis factor;

[12] a gene therapy method comprising the step of administering a body with a primary cultured adipocyte, which stably holds a foreign gene encoding a desired therapeutic protein that is secreted outside of a cell;

[13] a method of releasing a protein into the blood flow, wherein the method comprises the step of administering a body with a primary cultured adipocyte that stably holds a foreign gene encoding a protein that is secreted outside of the cell;

[14] the method of [13], which is a method for releasing the protein into the blood flow for 20 days or more;

[15] a method for lowering blood glucose, wherein the method comprises the step of administering a body with a primary cultured adipocyte, which stably holds a gene encoding insulin or glucagon-like peptide 1 (GLP-1); and

[16] an animal, the body of which is implanted with a primary cultured adipocyte that stably holds a foreign gene that encodes a protein secreted outside of a cell.--

Please amend the paragraph on page 9, line 24 through page 10, line 15, beginning, "The adipocytes for gene therapy of this invention are..." as follows:

--The adipocytes for gene therapy of this invention are particularly useful as cells for releasing proteins, that are encoded by foreign genes carried by the cells, into the blood flow. The proteins released into the blood flow include desired secretory proteins that demonstrate activity in the blood stream or at the surface of cells of target tissues, and examples include desired humoral factors such as hormones and cytokines, and antibodies. More specific examples are, as mentioned above, hypoglycemic hormones such as insulin and/or glucagon-like

peptide-1 (GLP-1) for treating diabetes and such; blood coagulation factors for treating hemophilia and such; and solubilized fragments of TNF-α receptor or ~~artificially solubilized~~ anti-TNF-α antibody (including antibody fragments that comprise an antibody variable region, such as Fab and scFv) in the treatment of diseases exhibiting enhanced TNF-α levels, such as rheumatoid arthritis. For example, for insulin, the cleavage sites (site 1 and site 2) can be substituted with the cleavage sequence of a protease expressed in adipocytes, so that mature insulin can be efficiently produced (for example, Groskreutz, D.J., *et al.* JBC, 1994, 269(8), 6241). An insulin analogue modified to a single chain may also be used (Lee, H.C., *et al.*, Nature. 2000 Nov 23, 408(6811):483-8). For GLP-1, a desired peptide that acts as a ligand for the GLP-1 receptor may be used (NP_002053; Thorens, B. *et al.*, Diabetes 42, 1678-1682 (1993); Dillon, J.S. *et al.*, Endocrinology 133, 1907-1910 (1993); Graziano, M.P. *et al.*, Biochem. Biophys. Res. Commun. 196, 141-146 (1993); Stoffel, M. *et al.*, Diabetes 42, 1215-1218 (1993)). An example is GLP-1(7-37) (Diabetes, 1998, 47:159-69; Endocrinology, 2001, 142: 521-7; Curr. Pharm. Des., 2001, 7:1399-412; Gastroenterology, 2002, 122:531-44).--

Please amend the paragraph on page 32, line 24 through page 33, line 18, beginning, "A nucleotide sequence with a total of 156 base pairs was designed, ..." as follows:

--A nucleotide sequence with a total of 156 base pairs was designed, comprising a sequence (SEQ ID NO: 10 shows the coding sequence; SEQ ID NO: 11 shows the amino acid sequence) in which human GLP-1 (7-37) and a stop codon are linked to the signal peptide (17 amino acids) of the PLAP gene used in Example 3. Nucleotides were synthesized so that a 22mer overlap was comprised at the center (sPL-GLP-1Fw and sPL-GLP-1Rv in Table 1). These were annealed and a double strand was formed using Pfu polymerase (Stratagene). The target fragment was then amplified by PCR using 5'-end and 3'-end primers (GLP-5' and GLP-3' in Table 1). This fragment was subcloned into pCR2.1 vector, then

excised using restriction enzymes, and subsequently inserted into pBabeCLXI2G vector, as in Example 3 (pBabeCL(sPL-GLP1)I2G). This was transfected into 293-EBNA cells by a method similar to that of Example 6, producing a GLP-1-expressing retroviral vector (MLV(VSV)/pBabeCL(sPL-GLP-1)I2G). Approximately 90 mL of the culture supernatant of 293-EBNA cells from nine 10-cm dishes was collected. Insoluble material was removed by centrifugation/filtration treatment, and the supernatant was then ultracentrifuged (19,500 rpm, 100 minutes) to yield a concentrated virus solution. This was transducted into primary cultured adipocytes (derived from C57BL/6 subcutaneous fat) that had been plated onto a 6-well plate the previous day. The transfected adipocytes were again plated onto a 12-well plate, and differentiation induction was carried out according to the method of Example 1. "Non-induced" refers to a condition in which culture was continued in a normal medium instead of in an induction medium or mature medium. Seven days later, the medium was exchanged to FCS-free DMEM medium comprising 1 mM Valine-pyrrolidine (GLP-1 degradation enzyme inhibitor; synthesized at Eisai). The culture supernatant was collected 18 hours later, and the amount of active GLP-1(7-37) was measured using ELISA (LINCO).--

Please amend the paragraph on page 33, line 31 through page 34, line 8, beginning, "After culturing the AP-expressing adipocytes (transducted with..." as follows:

--After culturing the AP-expressing adipocytes (transducted with MLV(VSV)/pBabeCL(PLAP)IP; derived from C57BL/6 subcutaneous fat) produced by the method of Example 3 to confluency, the cells were collected by trypsin treatment, washed with PBS, and suspended at ~~5x 10^7~~ 5x 10^6 cells/mL in ice-cold Matrigel (Becton Dickinson). Implantation was performed by injecting this to the dorsal subcutaneous area (Sc) of C57BL/6 mice (eight weeks old at the time of operation; Charles River) at a dose of 0.2 mL per mouse (1x 10^6 cells/head) (without differentiation induction). On the other hand, the same cells

were cultured to confluency, then cultured for three days in the inducing medium of Example 1, and then implanted by similar methods (with differentiation induction). Blood was collected over time by the method indicated in Example 2, and AP activity in the plasma was measured.--

Please amend the paragraph on page 37, line 22 through page 38, line 1, beginning, "The AP-expressing adipocytes produced in Example 3 (transfected..." as follows:

--The AP-expressing adipocytes produced in Example 3 (transfected with MLV(VSV)/pBabeCL(PLAP)IP; derived from ICR subcutaneous fat) were cultured to confluency. The cells were cultured for three days in the induction medium indicated in Example 1, and then collected by trypsin treatment. After washing with PBS, the cells were suspended at ~~5x 10^7~~ 5x 10^6 cells/mL into Matrigel. A five-fold stepwise dilution was carried out on the AP cell suspension solution using Matrigel, and ~~1x 10^7~~ 1x 10^6 cells/mL and ~~2x 10^6~~ 2x 10^5 cells/mL solutions were respectively prepared. bFGF was added to these solutions at a final concentration of 1 μg/mL, and they were then implanted to the dorsal subcutaneous area of ICR nude mice at a dose of 0.2 mL per mouse (high dose: 1x 10^6 cells/head; medium dose: 2x 10^5 cells/head; low dose: 4x 10^4 cells/head). As a control, GFP-expressing adipocytes were similarly treated, and were implanted into the subcutaneous tissue under the same conditions as for high-dose conditions (1x 10^6 cells/head).--

Please amend the paragraph on page 38, line 26 through line 36, beginning, "The MLV(VSV)/pBabeCL(s1s2B10Ins)I2G-transfected adipocytes..." as follows:

--The MLV(VSV)/pBabeCL(s1s2B10Ins)I2G-transfected adipocytes produced in Example 6 were subjected to differentiation induction stimulation using the same method as in Example 10, and then suspended at ~~5x 10^7~~ 5x 10^6 cells/mL in Matrigel to which 1 μg/mL of bFGF had been added. This suspension solution was implanted in the dorsal subcutaneous area of each diabetic mouse, at

0.2 mL per site, to a total of four sites (four x 10^6/head). For the control group, non-gene-transferred adipocytes were implanted by the same method. Implantation was performed 19 days after STZ treatment, and thereafter, FBG level was measured over time. Statistical analysis was carried out by comparison with the control group (unpaired t test).--

Please cancel the present "SEQUENCE LISTING", pages 1/7-7/7, and insert therefor the accompanying paper copy of the Substitute Sequence Listing, page numbers 1 to 4, at the end of the application.